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**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology (OSE)**
**Office of Pharmacovigilance and Epidemiology (OPE)**

# Epidemiology: Review of published study

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| Date: | March 18, 2015 |
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| Subject | Acetaminophen use in pregnancy and ADHD in offspring. |
| Drug Name(s): | Acetaminophen |
| Applicant/sponsor: | Multiple |
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## EXECUTIVE SUMMARY

This review evaluates the study published by Thompson et al that assessed a previously reported association between prenatal acetaminophen (APAP) use and risk of attention deficit hyperactivity disorder (ADHD) in the offspring. On January 9, 2015, FDA issued a Drug Safety Communication (DSC) regarding use of analgesics during pregnancy, which included discussion of a study by Liew and colleagues finding an association between prenatal exposure to APAP and subsequent ADHD. In response to the publication of that study, the investigators of the Aukland Birthweight Collaborative Study analyzed their study data on exposure to APAP in utero and subsequent behavior difficulties. Behavioral endpoints were assessed using the Strengths and Difficulties Questionnaire and the Conners Behavior Rating Scale, obtained when the children were 7 and 11 years old. Nearly half of the mothers in the study reported using APAP during pregnancy. Some differences in the rating scale scores between APAP-exposed and unexposed children were consistent with the direction of the finding in the Liew study, though the data could not provide a meaningful analysis of the risk of ADHD as a clinical disorder. The present study provides some level of support to the previously reported association, though whether the association is causal in nature is still uncertain. Preclinical data may be more informative in that regard. Preclinical findings on pregnancy exposure to APAP and neurodevelopment should be reviewed; additional reproductive toxicology experiments may be desirable.

## 1 INTRODUCTION

The Division of Nonprescription Drug Products (DNDP) requested the Division of Epidemiology 1 (DEPI1) review of a publication showing an association between acetaminophen (APAP) use during pregnancy and symptoms of attention deficit hyperactivity disorder (ADHD) in the exposed offspring. This review is in follow-up to the DEPI1 consultation of May 15, 2014, by Dr. Lockwood Taylor, covering previous studies of this same association.

### 1.1 BACKGROUND

Acetaminophen is a widely used analgesic and antipyretic available as without a prescription. The product is also marketed as a component of combination prescription products. It is widely used during pregnancy; in one U.S. study, 65% of mothers reported taking APAP while they were pregnant.[1]

Attention deficit hyperactivity disorder (ADHD) is a relatively common disruptive behavior disorder that presents in childhood. Various studies have examined prenatal factors as risk factors for ADHD.[2] Those factors reported to be associated with subsequent ADHD include maternal smoking and alcohol use during pregnancy, prenatal maternal stress, viral rash during pregnancy, low birth weight, polychlorinated biphenyl and lead exposure,[3] paternal smoking during the pregnancy,[4] maternal age,[5] and (relevant with respect to APAP use) maternal urinary tract infection.[6]

On January 9, 2015, FDA issued a Drug Safety Communication (DSC) regarding use of analgesics during pregnancy.[7] Among the observational studies described in that Drug Safety Communication was a study by Liew and colleagues finding an association between prenatal exposure to APAP and subsequent ADHD.[8] The DSC noted that FDA judged the findings from the Liew study and from two previous studies of this same association (by Streissguth and colleagues [9] and by Brandlistuen and colleagues[10]) to be inconclusive overall. Please refer to the May 15, 2014 DEPI 1 consult for a detailed review of these studies.



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With respect to biologic plausibility, Liew and colleagues speculated that the effect they observed might stem from endocrine disrupting properties of APAP. A recent study reported behavioral differences in adult mice exposed to APAP in the neonatal period.[11]

# 2 REVIEW METHODS AND MATERIALS

This review discusses the study by Thompson et al.:

- Thompson JMD, Waldie KE, Wall CR, Murphy R, Mitchell EA, et al. (2014) Associations between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years. PLoS ONE 9(9): e108210.

As this was a published study, there was no access to a complete study report.

# 3 REVIEW RESULTS

## 3.1 STUDY OVERVIEW

This study from Aukland, New Zealand, analyzed data from the Aukland Birthweight Collaborative Study (ABC), a prospective study of 871 children followed from birth through age 11 years, with enhanced sampling for small for gestational age (SGA) infants. As part of this study, investigators obtained information on use of analgesics during the pregnancy from the mothers shortly after birth and obtained behavioral symptom ratings on the offspring at ages 7 years and 11 years. Roughly half of the mothers reported using APAP during the study. The investigators found higher scores on the Strengths and Difficulty Questionnaire and on the Conners Parent Rating Scale (Revised) among children exposed to APAP in utero, consistent with an increase in ADHD behavioral symptoms, compared to children without prenatal APAP exposure. Use of other analgesics during pregnancy was not associated with such an increase in behavioral symptoms.

## 3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The objective was to assess the association between prenatal exposure to acetaminophen and other commonly used drugs and ADHD. The motivation for conducting the analysis was to test the association Liew et al. recently reported.

## 3.3 STUDY METHODS

### 3.3.1 Design & Setting

#### 3.3.1.1 Study Type

This was a prospective, longitudinal study.

#### 3.3.1.2 Population & Time Period

The subjects of the Aukland Birthweight Collaborative Study were children born from October 1995 to November 1997 in the Aukland District Health Board catchment area, or born from October 1995 to August 1997 in the Waitemata District Health Board catchment area.

#### 3.3.1.3 Selection, Inclusion and Exclusion Criteria

During the study period, the investigators recruited all small for gestational age (SGA) infants (in the tenth percentile) and an approximately equal number of other infants selected at random.



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Premature infants, those with major congenital abnormalities, and multiple birth infants were excluded. The original sample included 1714 infants, of both European and non-European ethnicity, but the investigators decided to exclude all non-European children after the 3.5 year assessment because of low participation by that subgroup.

#### 3.3.1.4 Protected Health Information (PHI) Requirements

The local ethics committee approved the study. Consent was obtained from the parents and assent from the children.

### 3.3.2 Outcome & Exposure

Interviewers asked the mothers shortly after birth, "Did you have any of these medicines or treatments during your pregnancy?" referring to a list which included anti-inflammatories, aspirin-based pain killers (e.g. Aspro, Disprin), other pain killers e.g. Panadol (acetaminophen), antibiotics and antacids. Accordingly, exposure was a dichotomous (yes/no) measure, irrespective of timing during the pregnancy. A mother could have answered "yes" to "other pain killers" (the APAP category) for a pain relieving medication other than APAP, since the question lacked specificity.

Assessments included a mailed questionnaire at age 1 year and study visits at ages 3.5, 7 and 11 years. Behavioral assessments included the Strengths and Difficulties Questionnaire (SDQ) completed by the parent at 7 and 11 years, and by the child at 11 years, along with the Conners Behavior Rating Scale (revised, long format) (CRS:R-L), completed by the parent at 7 and 11 years. Relevant subscales of these instruments were available for analysis (see below). Higher scores on these ratings indicate more symptomatology, except on the "Prosocial" SDQ subscale which is not included in the SDQ "Total Difficulties" score.

### 3.3.3 Covariates

The multivariable generalized linear model adjusted for the following covariates (as listed in the publication):

> SGA status, sex, age mother left school, maternal smoking during pregnancy, paternal smoking during pregnancy, marital status at birth, parity, socioeconomic status, maternal pre-pregnancy BMI, maternal stress in the last month of pregnancy, alcohol consumption in the first trimester, living with the child's biological father at 3.5 and child activity levels at 3.5, high fever during pregnancy, visiting GP for psychological conditions including depression and anxiety, taking medication during pregnancy for psychological conditions.

Family history of ADHD was not known.

### 3.3.4 Sample Size/Power

On the SDQ, there were 587 children with data at 7 years (representing 34% of the original sample of 1714 infants) and 614 at 11 years (36% of the original sample). On the Conners scale, there were 575 children with data at 7 years (34% of the original sample) and 617 at 11 years (36% of the original sample).

### 3.3.5 Statistical Analyses

The investigators analyzed mean behavioral rating scores of exposed and unexposed children at 7 and 11 years with multivariable generalized linear models, yielding 95% confidence limits for the difference in scores between exposed and unexposed children. Presumably, for the APAP



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analysis, children unexposed to APAP might have been exposed to other medicines that were inquired about, but this was not explicitly stated in the paper. A secondary analysis used log transformed score data. Another secondary categorical analysis used a cutoff threshold on the SDQ for defining abnormal behaviors.

### 3.4 STUDY RESULTS

The prevalence of pregnancy exposures in the sample was reported as follows (the timepoint was unspecified):

APAP—50%
Aspirin—5%
Antacids—17%
Antibiotics—24%

Compared to unexposed children, in an unadjusted analysis, APAP-exposed children had significantly higher scores on the SDQ (at 7 years and 11 years), indicating more behavioral issues. There were no statistically significant differences on the SDQ for the other drug exposures, which the investigators did not include in the adjusted analysis.

The following two tables display the adjusted analyses. On the SDQ, APAP exposed children had statistically significant higher scores overall on the 7-year parent and the 11-year child ratings, along with elevations on certain other scales as shown.

**Table 1. Adjusted difference in SDQ scores (APAP exposed group minus unexposed) with 95% confidence intervals.**

| Scale | Parent SDQ, 7 yr | Parent SDQ, 11 yr | Child SDQ, 11 yr |
|---|---|---|---|
| Total difficulties | **1.1 (0.2, 2.0)** | 0.8 (-0.1, 1.8) | **1.1 (0.2, 2.0)** |
| Emotion | **0.4 (0.0, 0.7)** | **0.5 (0.1, 0.9)** | 0.2 (-0.2, 0.6) |
| Conduct | **0.2 (0.0, 0.5)** | 0.0 (-0.3, 0.3) | **0.3 (0.0, 0.6)** |
| Hyperactivity | 0.4 (-0.1, 0.8) | 0.1 (-0.3, 0.6) | **0.4 (0.0, 0.8)** |
| Peer Esteem | 0.1 (-0.2, 0.4) | 0.2 (-0.1, 0.5) | 0.2 (-0.1, 0.5) |
| Prosocial | -0.1 (-0.5, 0.2) | -0.1 (-0.4, 0.3) | 0.0 (-0.3, 0.3) |

The next table shows the adjusted differences in the Conners rating scores at 7 and 11 years. There were some statistically significant elevations with APAP exposure, as shown, but only on the 7 year ratings, and not on the ADHD index score.



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**Table 2. Adjusted differences in parent's Conners rating scores (APAP exposed group minus unexposed) with 95% confidence intervals.**

| Scale | 7 years | 11 years |
|---|---|---|
| Conners ADHD index | 1.5 (-0.1, 3.0) | 0.5 (-1.1, 2.1) |
| CGI restless-impulsive | **2.1 (0.4, 3.7)** | -0.1 (-1.7, 1.6) |
| CGI emotional lability | **3.0 (1.3, 4.7)** | 0.6 (-1.1, 2.4) |
| CGI total | **2.6 (1.0, 4.2)** | 0.1 (-1.5, 1.8) |
| DSM IV inattentive | 0.7 (-0.8, 2.2) | 0.2 (-1.5, 1.9) |
| DSM IV- hyperactive impulsive | **2.0 (0.3, 3.6)** | 1.3 (-0.2, 2.7) |
| DSM-IV total | 1.5 (-0.1, 3.0) | 0.8 (-0.7, 2.3) |
| DSM inattentive symptoms | 0.0 (-0.2, 0.1) | 0.0 (-0.2, 0.2) |
| DSM hyperactive-impulsive symptoms | **0.2 (0.0, 0.4)** | 0.1 (-0.1, 0.2) |

While there were some statistically significant increases in these measures associated with APAP exposure, there were no statistically significant decreases, as might have been expected with multiple comparisons if due to chance.

The secondary analysis used a cutoff score on the SDQ for defining abnormal behavior appeared generally underpowered: with APAP exposure, the OR for an abnormal SDQ parent score at 7 years was 2.1 (95% CI 0.0-5.0), for an abnormal parent SDQ at 11 years, 1.2 (0.6-2.5), and for child SDQ at 11 years, 1.0 (0.6, 1.6).

In unadjusted analyses, there were no statistically significant differences in SDQ Total Difficulty scores with pregnancy exposures to anti-inflammatories, aspirin, antacids, or antibiotics (data not shown).

### 3.5 STUDY CONCLUSIONS

The investigators stated their conclusions as follows: "These findings strengthen the contention that acetaminophen exposure in pregnancy increases the risk of ADHD-like behaviours. Our study also supports earlier claims that findings are specific to acetaminophen."

## 4 DISCUSSION

Strengths of the study include the fact that the mothers reported pregnancy exposures soon after the birth of the child, mitigating the possibility that mothers of children with behavioral problems would be biased towards recalling APAP use. A strength of the analytic method is that it adjusted for many ADHD risk factors to reduce possible confounding, though parental history of ADHD was not known. It was particularly important that the analysis adjusted for occurrence of high fever during the pregnancy, which could be a confounder in the classic manner of influencing both the developmental outcome and the use of APAP. The length of follow up time (up to 11 years of age) was sufficient to allow for the emergence and detection of behavioral problems, and the behavioral assessments (SDQ and Conners) were reasonable screening tools. The fact that pregnancy exposures to other commonly used medications did not appear to affect the behavioral assessments provides some specificity to the associations observed with APAP, though the APAP exposed children formed the largest sample.



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The major limitation of this study is that it analyzes differences in behavioral rating scales rather than the prevalence of ADHD as a clinical disorder among children exposed to APAP in utero, or a proxy for such a clinical disorder such as ADHD medication use as in Liew et al. Small mean differences in behavioral ratings may have statistical significance despite being of unknown clinical significance. Additionally, some of the scales on the SDQ do not appear to be directly relevant to ADHD. The authors attempted a categorical analysis using clinically significant cutoff scores, but it was underpowered. Other limitations include lack of information on quantity of exposure and timing of exposure during pregnancy, and the fact that prenatal exposure to other medications was not adjusted for in the analysis. Limiting the sample to children of European ancestry compromises the generalizability of the study. Also, there may have been some misclassification of exposure. Consumers of combination over-the-counter products do not always realize that APAP is contained in the products they use, plus mothers were simply asked about their use of "other painkillers" such as APAP. Finally, while the investigators made every effort to adjust for confounding, we do not know if this was fully successful, and conditions that led the mothers to require APAP during their pregnancy could have had neurodevelopmental impacts in the offspring.

## 5 CONCLUSION

The investigators initiated this analysis within their existing study in response to the publication of the Liew study. While the present study has the limitations described above and was not designed to assess this particular association, the directionality of the differences in the behavioral ratings following prenatal APAP exposure is consistent with two previous studies reporting a similar association (Liew et al. and Brandlistuen et al.), though a fourth study (Streissguth) did not find an association. Whether the association is causal in nature remains uncertain.

## 6 RECOMMENDATIONS

The existing preclinical data on pregnancy exposure to APAP and exposure of juvenile animals to APAP regarding neurodevelopment should be assessed. Additional reproductive toxicology experiments may be needed, since these are likely to be more feasible than undertaking additional longitudinal studies of child development.

There are now three studies pointing towards attentional difficulties in children following in utero exposure to APAP (though it would have to be said that the present study is the methodologically weakest of the three). Additional long term studies of behavioral development in children following prenatal exposure to APAP would certainly be useful, but would not provide direct evidence of causality. Preclinical data may be more informative in that regard.

**APPENDIX TABLE – DESIGN SUMMARY**

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|---|---|
| 1.1 Objectives/Aims/Scope | To assess the reported association between prenatal exposure to APAP and ADHD. |
| 1.2.1 Design | |
| 1.2.1.1 Type | Longitudinal cohort study |
| 1.2.1.2 Data Source | Aukland Birthweight Collaborative Study |
| 1.2.1.3 Time Period | Children born from Oct. 1995 to Nov. 1997 |
| 1.2.1.4 Criterion (Selection) Standards | In the catchment area, all small for gestational age (SGA) infants (in the tenth percentile) and an approximately equal number of other fullterm infants selected randomly |
| 1.2.2 Setting | Two District Health Board regions in New Zealand |
| 1.2.3 Exposure/Intervention | Prenatal exposure to APAP (yes/no) |
| 1.2.4 Outcome(s) | Strengths and Difficulties Questionnaire (SDQ) and Conners Behavior Rating Scale, obtained at 7 and 11 years of age |
| 1.2.5 Covariates | Included multiple known risk factors for ADHD |
| 1.2.6 Sample Size | N=614 for SDQ, N=617 for Conners |
| 1.2.7 Statistical Analyses | Multivariable general logistics model for difference in scores |
| 1.2.8 Study Results | Statistically significantly higher adjusted Total Difficulties scores on SDQ for APAP-exposed children. Elevations on some subscales of Conners but not on ADHD index. |



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